REMARKS

Applicants respectfully request reconsideration of the present application in view of the following comments.

I. Status of the Claims

No claim amendments are made in this response. Claims 1, 2, 4-22 and 25-54 are pending and under examination.

II. Rejection of Claims under 35 U.S.C. §102(a)

Claims 1, 2, 4-11, 13-22, 25-38, 41-43, 45, 46, 49, 50 and 53 are rejected under 35 U.S.C. §102(a) for alleged anticipation by PCT Publication No. WO 99/02665 by Liversidge et al. ("Liversidge"). Applicants respectfully traverse the rejection.

The claimed invention is directed to a solid dose controlled release nanoparticulate composition comprising: (a) a drug having an effective average particle size of less than about 1000 nm, (b) at least one surface stabilizer associated with the surface of the drug particles, and (c) at least one pharmaceutically acceptable high molecular weight rate-controlling polymer which is integrated in a rate-controlling matrix with the drug or which coats the drug.

A. The cellulosic surface stabilizer of Liversidge does not teach or suggest Applicants' claimed rate controlling polymer

Liversidge describes a nanoparticulate HIV protease inhibitor composition comprising a cellulosic surface stabilizer. *See* the abstract. The Examiner asserts that the cellulosic surface stabilizer of Liversidge's composition teaches the high molecular weight rate-controlling polymer of the claimed invention. *See* final Office Action, page 3, lines 3-4.

First, Liversidge does not teach or suggest that the cellulosic surface stabilizer is integrated into a matrix or coats the HIV drug particles to control the release rate of the drug.

Thus, one of skill in the art given the teaching of Liversidge would have no road map of how to modify Liversidge to obtain the claimed invention.

Second, the Examiner's argument that the cellulosic surface stabilizer of Liversidge's composition reads on the rate-controlling polymer of the claimed invention is flawed. This is because the Examiner fails to articulate which component of Liversidge's composition would have taught the surface stabilizer of the claimed invention, which is associated with the surface of the nanoparticulate drug particles. Applicants' claimed invention requires a surface stabilizer **and** a high molecular weight, rate controlling polymer. These two components are not the same.

B. The excipients of Liversidge do not teach or suggest Applicants' claimed high molecular weight, rate controlling polymer

Liversidge's composition may optionally comprise surfactants, binders, fillers, lubricants, disintegrants and other excipients. *See* page 7, 1st full paragraph. It is unclear which of these additional components the Examiner deems to read on the high molecular weight rate-controlling polymer of the claimed invention. *See* final Office Action, page 2, last full paragraph.

There is no teaching or suggestion in Liversidge that any of these additional components can control the drug release, let alone any teachings of the specific structural features recited in the claims regarding the rate-controlling polymer, i.e., integrated into a matrix with the drug or coating the drug.

Accordingly, Liversidge fails to teach each and every aspect to anticipate the claimed invention.

III. Rejection of Claims under 35 U.S.C. §103(a)

Claims 1, 4-10, 12-18, 21, 22, 25, 26, 30, 32-35 and 37-54 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over U.S. Patent No. 4,665,081 to Doi et al. ("Doi") in view

of U.S. Patent No. 4,765,990 to Sugimoto et al. ("Sugimoto"). Applicants respectfully traverse the rejection.

According to the Examiner, Doi meets all claim recitations except for the particle size, and Sugimoto is cited for the alleged teaching of the particle size of less than 1000 nm. *See* final Office Action, pages 3 and 4. Applicants respectfully disagree.

First, neither Doi nor Sugimoto discloses a nanoparticulate active agent composition comprising a surface stabilizer associated with the surface of the active agent particles. In fact, a surface stabilizer is not required for either Doi's or Sugimoto's composition because the particle size of these prior-art compositions are large enough to maintain the stability of the composition. Neither reference discloses that a surface stabilizer is needed to prevent the particles of the active agent from agglomeration or aggregation.

Second, Doi teaches away from the claimed invention. Doi relates to a solid nifedipine preparation, which requires the specific combination of nifedipine with casein and one or more specific inorganic excipients. *See* column 3, lines 50-56. More specifically, Doi emphasizes that the crucial ingredients of the composition cannot be substituted, even by similar ingredients:

> *In the solid nifedipine preparation of this invention, it is* ***indispensable*** *for enhancing dissolution of nifedipine that the particulate composition has been obtained by subjecting nifedipine in mixture with casein and one or more inorganic excipients to co-pulverization. The specific dissolution-promoting effect* ***can not be expected*** *if the inorganic excipients used in this invention are replaced by similar other inorganic excipients such as aluminum silicate, calcium carbonate, alumina and silica gel. Similarly, such dissolution-promoting effect* ***can not be expected*** *if the three essential ingredients, i.e., nifedipine, casein and one or more of the inorganic excipients are separately pulverized and then mixed together, or even if any one of the three essential ingredients is separately pulverized and mixed with a co-pulverized mixture of the other ingredients.*

Column 4, lines 44-59, with emphasis added.

Moreover, Doi defines the specific content of the high molecular substance:

> *If the proportion of the enteric high molecular substance and/or the plasticizer to the co-pulverized mixture is outside the above defined range, the effect on inhibiting rapid dissolution of nifedipine, or in other words, on gradual release of nifedipine from the preparation for an prolonged period of time will be* ***minimized or lost****.*

Column 7, lines 9-14, with emphasis added.

Furthermore, in contrast to the claimed invention which comprises a high molecular weight rate-controlling polymer that coats the drug, Doi expressly recommends ***against*** coating the drug:

> *If the enteric coating on the conventional nifedipine preparation is damaged by mechanical shock or unexpected external force, it will no longer be possible to inhibit rapid dissolution of nifedipine. In the solid nifedipine preparation of this invention, however, the enteric high molecular substance and the plasticizer are* ***not coated*** *as a thin film on granules or tablets containing nifedipine so that there is no fear of damage of the thin film.*

Column 6, line 63, through column 7, line 3, with emphasis added.

Accordingly, contrary to the Examiner's assertion, one skilled in the art would not have generalized or modified Doi's composition to obtain the claimed invention.

Third, the secondary reference, Sugimoto, fails to compensate for the acknowledged deficiency in the particle size. Sugimoto describes a granulation or fine granulation process to obtain a nifedipine composition "having an average particle size of not more than 5μ, preferably 1 to 4μ." Column 3, lines 6-9 and 68. Even if the teaching of Sugimoto is combined with that of Doi, the prior art fails to render the claimed composition, which has an effective average particle size of less than 1000 nm, obvious.

Moreover, Sugimoto compares the blood level of nifedipine when nifedipine compositions having different particle sizes were administered. *See* Figure 2 and column 3, lines 22-40. Specifically, when the particle size of Sugimoto's composition was reduced from 9.6μ to 5.0μ (a 1.92-fold decrease in the particle size), the blood level of nifedipine had a large increase, comparing curve b (composition having a 5μ particle size) and curve iii (composition having a 9.6μ particle size) in Figure 2. In contrast, when the particle size of Sugimoto's composition was further reduced from 5.0μ to 2.1μ (a 2.38-fold decrease in the particle size), the blood level of nifedipine had only a small increase, reflected by the closely parallel curve a (composition having a 2.1μ particle size) and curve b in Figure 2. In fact, Sugimoto does not distinguish the composition having a 5μ particle size from the composition having a 2.1μ particle size, but concludes that the composition having a 9.6μ particle size "is inferior in both the absorbability and the release sustaining properties" (column 3, lines 38-40).

In light of the results disclosed by Sugimoto, one skilled in the art would not have any reason to further reduce the particle size of Sugimoto's composition to much less than 2.1μ, let alone to a particle size of less than 1000 nm, as required by the claimed invention.

Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: June 8, 2010

By 

FOLEY & LARDNER LLP
Customer Number: 31049
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Applicant
Registration No. 34,717